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| EXAMINER | |
|---|---|
| UNGAR, SUSAN NMN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 09/684,599 | **Applicant(s)** PASTAN ET AL. | |
|---|---|---|---|
| | **Examiner** Susan Ungar | **Art Unit** 1642 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 15 December 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *19-32*.
   Claim(s) withdrawn from consideration: *none*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Susan Ungar
Primary Examiner
Art Unit: 1642

Continuation of 3. NOTE: The addition of the limitations drawn to an isolated peptide having 90 identity over a comparison window of about 10-20 amino acid residues raises new issues and requires further consideration and/or search.

Continuation of 11. does NOT place the application in condition for allowance because:

If the amendment to the claims were to be entered, claims 20-25, 27-32 would still be rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in the action mailed August 25, 2004, Section 4, pages 2-5

Applicant argues that the claims as currently constituted are not drawn to vaccines, but rather are drawn to isolated proteins and peptides. Further, the claimed proteins and peptides are useful, for example, to raise antibodies which are useful for detecting the presence of mesothelin and the action neither alleges nor shows that raising antibodies by the claimed proteins and peptides is not an appropriate utlity or is not enabled. Applicant reminds Examiner that a composition requires only one utility to be patentable and that it only need be enabled for that utility.

The argument has been considered but has not been found persuasive. Examiner reminds Applicant that the rejection in Section 4, pages 2-5 is not a utility rejection, but rather an enablement rejection. As previously set forth, the claimed invention reads on anti-cancer vaccines and Applicant's previous amendment to the claims, to delete the term "vaccine" does not alter that fact. Although no longer specifically recited in the claims, the vaccine limitation is inferred by the claim language because the claims are specifically drawn to the use of the claimed peptides and proteins as immunogens (which reads specifically on in vivo administration) for patients with mesothelioma-or ovarian cancer-cells expressing mesothelin, given the understanding in the art that T-cells generated by vaccines will recognize, ex vivo the immunogen use to produce them in vivo, as well as the understanding in the art that administration of peptide vaccines results in not only a humoral but also a cellular immune response wherein both antibodies and T-cells are produced. Further, given the clear teachings of the specification that the antibodies raised by the immunogens of the invention would be useful in inhibiting the spread or implantation of ovarian cancer cells in the peritoneal wall, given the teaching in the specification that the administration of peptides is well known for treatment of a variety of diseases, given the teaching that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin with mesothelin peptides, given the specific teaching in the specification of vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of tumors, it is reasonable to infer from the claims as currently constituted that the claims are in read on anti-cancer vaccines for the treatment of mesothelioma-or ovarian cancer cells and that these limitations are encompassed by the claims and for the reasons of record, the claims are not enabled. Finally, although Applicant suggest that the claimed invention, SEQ ID NO:2 and variants thereof, is useful for the production of antibodies to be used for detecting the presence of mesothelin in a biological sample and for targeting cytotoxins to cells expressing mesothelin, given that the only useful function disclosed in the specification is apparently for the diagnosis and treatment of cancer, one would not know how to use the claimed invention if it were not used for the methods contemplated in the specification. If indeed there is no differential expression of SEQ ID NO:2 in cancer and normal tissues, one would reasonably wonder why would one make antibodies to target cytotoxins to normal tissues and what one would one use information about the detection of SEQ ID NO:2 in a biological sample for except, perhaps, for experimental reasons. Further, Applicant appears to admits on the record that the specific function of SEQ ID NO:2 is unknown (see response, page 9,first full paragraph). In particular, Applicant argues that a rejection drawn to the effects of amino acid alteration in the claimed variants on the function of SEQ ID NO:2, even if a function for SEQ ID NO:2 were known, might have merit if the claims under rejection recited a protein with, for example, with an enzymatic or therapeutic activity but has little apparent application to the claims actually presented and is without merit because the claims are not drawn to proteins or peptides that have a delicate or special activity that might be unpredictably destroyed by a single mutation, they need only be capable of raising antibodies to the protein of SEQ ID NO:2. Thus, if the claimed invention is not useful for the diagnosis or treatment of cancer, one would not know how to use the claimed invention. Given Applicant's line of argument, it appears that Applicant's is suggesting that the claimed invention does not have utility and Applicant's reference to "utility" reinforces this appearance. However, as set forth above, the rejection of the claims is a rejection under 35 USC 112, first paragraph and for the reasons set forth previously and above, the invention is not enabled. Applicant's arguments have been considered but have not been found persuasive and the rejection is maintained.

If the amendment to the claims were to be entered, claims 20-25, 27-32 would still be rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in the action mailed August 25, 2004, Section 5, pages 5-18

Applicant argues that there is no requirement in the recitation of the claims that the variants of the protein or of the mesothelin fragments be expressed on a cell. The argument has been considered but has not been found persuasive since as set forth previously and above, the claims as currently constituted read on an anti-cancer vaccine for treatment and if the variants of the protein or of the mesothelin fragments are not expressed on any cells, including cancer cells, there would be no reasonable expectation of success using the claimed invention.

Applicant argues that the recitation of proteins and peptides which have a defined degree of sequence identity to a particular novel protein and which retain a particular function is a common claim format.

The argument has been considered but has not been found persuasive because although the claim language may be conventionally used, Examiner reminds Applicant that each case is examined on its own merits. Further, given that the claimed variants are unknown, and as set forth above, the claims as currently constituted read on anti-cancer vaccines for treatment and the specification does not in fact teach any variants or teach which or in fact whether any variants would be targets for the inferred vaccine even if SEQ ID NO:2 is found to be an appropriate cancer vaccine target and therefore the claims drawn to SEQ ID NO:2 are enabled, it is clear that this finding cannot be extrapolated to the claimed variants for the reasons of record. Further, it is noted that Applicant does not address the issue raised as to whether or not the claimed variants in fact exist or that antibodies or T-cells against those variants could be successfully used as immunogens for the functions as inferred and claimed. This issue is critical, given the novel nature of the instant invention and the teachings of MPEP 2164.03.

Applicant argues that whether or not antibodies raised by any particular protein or peptide actually bind to SEQ ID NO:2 can be easily accomplished by standard immunoassays such as ELISAs. If Examiner chooses to maintain this portion of the rejection, Applicants respectfully request that the Examiner explain why these standard techniques, in use for decades, would not be successful in

determining whether the antibodies raised would actually bind to SEQ ID NO:2.

The argument has been considered but has not been found persuasive because the standard for enablement under 35 USC 112, first paragraph is not whether the specification teaches how to screen for a particular moiety, but rather, how to make and use the claimed invention. In addition, as set forth previously and above, a vaccine treatment limitation is inferred by the claim language because the claims are specifically drawn to the use of the claimed peptides and proteins as immunogens (which reads specifically on in vivo administration) for patients with mesothelioma-or ovarian cancer-cells expressing mesothelin, given the understanding in the art that T-cells generated by vaccines will recognize, ex vivo the immunogen use to produce them in vivo, as well as the understanding in the art that administration of peptide vaccines results in not only a humoral but also a cellular immune response wherein both antibodies and T-cells are produced. Thus, the issue is not whether or not antibodies would bind to SEQ ID NO:2, but rather the issue is whether or not the variant immunogens which comprise segments of SEQ ID NO:2 present the undefined segments of SEQ ID NO:2 in such a manner that the invention can be successfully used in the manner inferred by the claims as currently constituted and as taught in the specification. In particular, the specification provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which epitopes are linear or 3-dimensional in the claimed variants of SEQ ID NO:2 wherein these variants are useful as the inferred anti-cancer vaccine. As set forth by Holmes and Greenspan et al, both of record, the art recognizes the unpredictability of the art. Again, the ability to screen does not meet the requirements of 35 USC 112, first paragraph because even if screening demonstrated that the antibodies produced bind to SEQ ID NO:2, this does not provide enablement for the claimed invention which reads on anti-cancer vaccines.

Applicant reminds the Examiner that the tertiary structure of a molecule is determined by its primary structure and therefore the tertiary structure of SEQ ID NO:2. Applicant argues that although it is possible that proteins with 90% sequence identity to SEQ ID NO:2 will have a different conformation and therefore different conformational epitopes, it is unlikely that they will not have portions that do not have linear or conformational epitopes that will raise antibodies that also to SEQ ID NO:2 and if they do not, they are not within the scope of the claims. Applicant reminds Examiner that claims are permitted to encompass inoperable embodiments so long as the practitioner can determine whether or not the embodiment is operable with no more effort than is normally used in the art and the practitioner can test any protein with tests commonly conducted in the art.

The argument has been considered but has not been found persuasive. It is noted that the claims are not drawn to 90% identity, but rather are drawn to proteins having, that is comprising, 85% identity to SEQ ID NO:2, peptides comprising 90% identity over a comparison window of about 10-20 amino acid residues, an isolated peptide comprising at least 10 contiguous amino acids of SEQ ID NO:2. As set forth previously and above, the specification provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which epitopes are linear or 3-dimensional in the claimed variants of SEQ ID NO:2 wherein these variants are useful as the inferred anti-cancer vaccine. Although the undefined variants might indeed produce a subset of antibodies that bind to SEQ ID NO:2, there is neither a teaching in specification nor in the art of record that the claimed undefined variants exist or even if they do exist and are differentially expressed on cancer cells as compared to normal cells, whether these undefined variants would be useful targets for the inferred anti-cancer vaccine, that is whether the undefined variants that comprise segments of SEQ ID NO:2 present the undefined segments of SEQ ID NO:2 in such a manner that the invention can be successfully used in the manner inferred by the claims as currently constituted and as taught in the specification.

Applicant argues that peptides that are fragments of SEQ ID NO:2 or that share 90% identity with such fragments may well only relate to linear epitopes, not conformational epitopes and that linear epitopes are useful for example to bind to denatured protein of SEQ ID NO:2 in SDS-PAGE and Western blots and Applicant is unaware of any requirement of the patent law that the claimed peptides have to also raise antibodies against conformational epitopes.

The argument has been considered but has not been found persuasive, because contrary to Applicant's arguments, the claims are not drawn to peptides that are fragments of SEQ ID NO:2 or that share 90% identity with such fragments, but rather are drawn to undefined peptides which comprise 10 or more contiguous amino acids of SEQ ID NO:2 and peptides having (that is comprising) 90% sequence identity over a comparison window of about 10-20 amino acid residues of SEQ ID NO:2.

Applicant further argues that Bowie, Burgess, Lazar, Scott and Bork references are not relevant to the instant rejection since these references relate to the biological activity of proteins. Upon review and reconsideration, Examiner is pursuaded and hereby withdrawns the grounds of rejection drawn to Bowie, Burgess, Lazar, Scorr and Bork

Applicant further argues whether or not antibodies raised by any particular protein or peptide actually binds to SEQ ID NO:2 can easily be accomplished by standard immunoassays such as ELISAs and Examiner is asked to explain why these standard techniques would not be succesful in determining whether the antibodies raised would "actually bind to SEQ ID NO:2" The argument has been considered but has not been found persuasive. As set forth above, the enablement requirement is not drawn to how to screen, but rather is drawn to how to make and use. Given the inferred use of the claimed invention, given the breadth of the claims, in the absence of a teaching of which epitopes of SEQ ID NO:2 in the highly variant claimed genus are exposed on the surface of the protein, the specification does not teach how to make the claimed invention.

Applicant further argues that it is unlikely that proteins with 90% identity to SEQ ID NO:2 will have a different conformation than SEQ ID NO;2 and therefore different conformational epitopes. The argument has been considered but has not been found persuasive for the reasons of record. It is noted that Applicant does not present this argument drawn to undefined peptides having at lesat 90% identity of at least 10 contiguous amino acids of SEQ ID NO:2, wherein in fact it could not be predicted that the peptides of undefined length would in fact have conformational eptiopes of SEQ ID NO:2.

Applicant further argues that these peptides may in fact have only linear epitopes which would be useful for western blot analysis. The argument has been considered but has not been found persuasive for the reasons previously set forth.

Applicant further argues that only 4 glycosylation points are found on SEQ ID NO:2 and the action presents no evidence to show that the rpesence of a few carbohydrates would prevent the generation of antibodies to other portion of the protein and further argues that the claims are permitted to encompass inoperable embodiments. The argument has been considered but has not been found persuasive because the issue raised here is drawn to the inferred use of the claimed invention and given the lack of teaching drawn to the broadly variant genus, one would not know how to make and use the claimed invention given the information in the specifciation as

originally filed and further for the reasons set forth previously and above drawn to inoperable embodiments.

Applicant further argues that Kirkin and Chaux are not relevant to the claims under examination since Kirkin is concerned exclusively with melanoma-associated antigens and Chaux concerns the development of an extremely sensitive immunoassay for detecting CTL precursors. The argument has been considered but has not been found persuasive because the references clearly delineate the state of the art at the time the invention was made. Further, the argument is not persuasive for the reasons of record. Applicant cites Jager et alSillman et al, Mayordomo et al, Paglia et al, Porgador et al. It is noted that neither the arguments drawn to the newly submitted references nor the references themselves have been considered for the reasons set forth above. Applicant further argues that pulsing or loading dendritic cells with antigen to prime T cells was known in the art at the time the invention was made and thus techniques already existed to break self-tolerance adequately to enable the invention as claimed. The argument has been considered but has not been found persuasive because the claims are not drawn to pulsed or loaded dendritic cells. APplicant further argues that Smith notes that anergy can be overcome in vitro by use of cytokines. The argument has been considered but has not been found persuasive because the claims read on in vivo treatment. Applicant further argues that Smith does not recite at page 484 that tumors progressively lose MHC representation at the sruvace of the cell and Examiner is requested to clarify the reference and Applicants respectfully note that the present claims are drawn to compositions, not methods and even if tumors lose MHC represenetation over time, that doe not diminish the value of raising a T cell response early in treatment and nothing in the patent statute requires that a composition be useful throughout the entire course of a disease. The argument has been considered but has not been found persuasive because although Applicant asks for clarification as to where the information is found in the Smith article, APplicant does not argue that the statement in the action is not true. Further, for the reasons previously set forth, one would not know how to use the claimed invention.

Applicant reiterates arguments drawn to dendritic cells and the newly submitted references. The arguments drawn to dendritic cells were considered above and not found to be persuasive for the reasons set forth above. Neither the arguments drawn to the newly submitted references, nor the references themselves have been considered for the reasons set forth above.

Applicant argues that Boon, Kirkin do not teach against the claimed invention and that Bowie, Burgess, Lazare, Scott do not remedy the lack of teaching of Boon and Kirkin. The argument has been considered but has not been found persuasive because the unpredictability of the art has been clearly delineated previously. Given the teaching in the specification as originalloy filed and the teachings known in the art, it could not be predicted that the claimed variants would also function to adeuatlely stimulate effective T-cell responses.

Applicant reiterates arguments drawn to the claims under examination recite compositions and not vaccines. The argument has been previously considered and has not been found persuasive for the reasons set forth above. Applicant reiterates arguments drawn to peptide loading on dendritic cells. The arguments were considered previously and have not been found persuasive for the reasons set forth previously.

If the Amendment were to be entered, Claims 19-26, 30-32 would not remain under 35 USC 112, first paragraph for the reasons previously set forward in the paper mailed August 25, 2004, Section 6, page 18.

If the Amendment were to be entered, claim 22 would not remain rejected undre 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 25, 2004, Section 7, page 19.

If the amendment were to be entered, claims 20-25 and 27-32 would remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 25, 2004, Section 8, pages 19-25.

Applicant argues that the findings in Lilly and Enzo do not relate to proteins and peptide. The courts recognize the degeneracy of the genetic code while amino acids constituting the sequence of proteins is not degenerate. In any case, the claims recite proeins and peptides have a defined degree of sequence identity to SEQ ID NO:2 which retain defined functions and such claims are routinely accepted by the Office as complying with the statutory requisities for patenting, including written description and the Action has presented no reason why the same treatment is not appropriate in this case.

The argument has been considered and has not been found persuasive because the courts have consistenty found that the fact patter in Lilly and Enzo can be extrapolated to molecular products other than polynucleotides and that the standards defined by the court decisions are applicable to both polynucleotides as well as polypeptides. The degeneracy or lack thereof of the genetic code or protein sequences is not the issue raised here is that the specification as originally filed does not structurally describe a representative number of the genus claimed, does not describe structural features common to the members of the genus which features constitute a substantial portion of the genus, does not disclose functional characteristics coupled with a known or disclosed correlation between function and structure.

If the amendment were to be entered, claim 19 would not remain rejected under 35 USC 112, second paragraph for the reasons previoiusly set forth in the paper mailed August 25, 2004, Section 9, page 25.

If the amendment were to be entered, claims 19-25, 27-32 would remain rejected under 35 USC 102(b) for the reasons previously set forh in the paper mailed August 25, 2004, Section 9, pages 25-27.

Applicant argues that Figure 3 does not show the presence of the CAK1 antigen in isolation. A western blot is designed to reveal the protein bound by the probing antibody without also revealing the presence of any number of other proteins that may be present but which are not bound by the antibody. The argument has been considered but has not been found persuasive, the specification, in particular defined the term "isolated" as efer to material which is substantially or essentially free from components which normally accompany it as found in its native state. Further, the specification does not define the terms substantially or essentially free and one of ordinary skill

would immediately understand that the protein isolated in a western blot is substantially and essentially free of components which normally accompany it as found in its native state.